Quick guide

Tolls

Ruslan Medzhitov

What are they? Tolls are a family of transmembrane receptors that play an essential role in sensing infection in mammals and insects. When Tolls bind to their ligands, they induce signaling pathways that lead to the elimination of the infecting pathogen.

What do they look like? Tolls have a large extracellular region composed of leucine-rich repeats, and a cytoplasmic signaling domain. The intracellular domain of Tolls is homologous to the corresponding region of the interleukin-1 receptor (IL-1R), this domain is called the Toll/IL-1R homology (TIR) domain.

What do they do? Mammalian Toll-like receptors (TLRs) defend against microbial infection. Activation of TLRs triggers inflammatory and antimicrobial responses, such as production of cytokines, antimicrobial peptides and nitric oxide. TLRs can also induce signals that activate adaptive immune responses mediated by T and B lymphocytes. *Drosophila* Toll-1 is a critical component of dorsal–ventral patterning in embryos. 18-Wheeler also plays a role in early fly development.

What do they recognize? Most of the known ligands of mammalian TLRs are conserved pathogen-associated molecular patterns (PAMPs). Well-known PAMPs are bacterial lipopolysaccharides, peptidoglycan and lipoteichoic acid. PAMPs are produced only by microbes so their recognition by Tolls signals infection. PAMPs are thought to bind directly to TLRs. This is not the case however for *Drosophila* Toll-1 which recognizes a proteolytic fragment of the endogenous protein Spatzle. The proteolytic cascade that generates active Spatzle is triggered upon recognition of a PAMP.

How do they signal? *Drosophila* and mammalian Tolls activate the conserved NF-κB signaling pathway (see Figure). Human TLRs signal through the adapter protein MyD88, which comprises a TIR domain and a death domain. The death domain of MyD88 interacts with the protein kinase IRAK. IRAK activates another adapter, TRAF6, and ultimately NF-κB. *Drosophila* Toll-1 engages a similar signaling pathway, except that a distinct death-domain-containing adapter protein called Tube is used as well as a MyD88-like adapter. Both of these adapters can interact with Pelle, the protein kinase homologous to IRAK.

Where can I find more?

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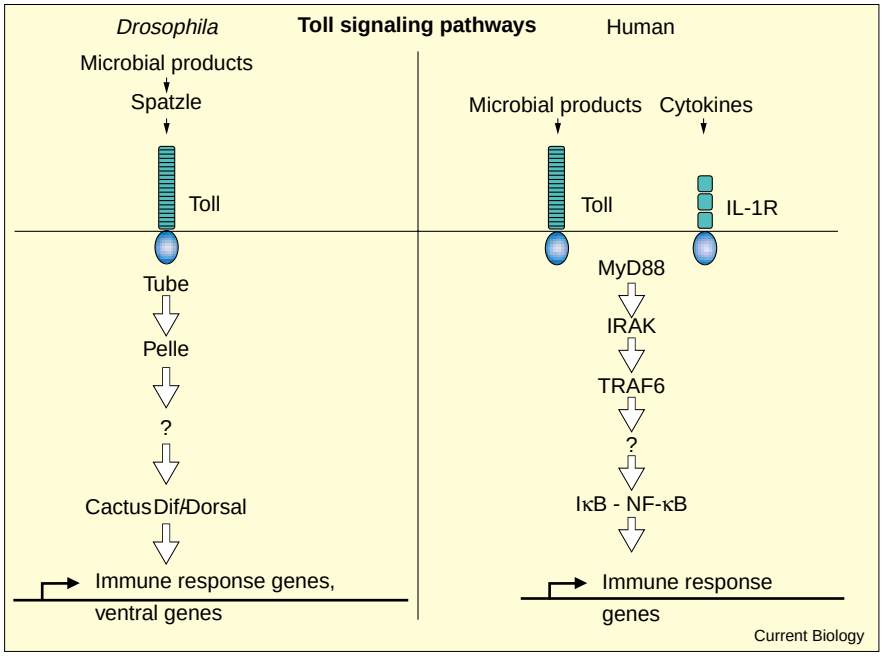
Address: Howard Hughes Medical Institute and Section of Immunobiology, Yale University Medical School, New Haven, CT 06520 USA.



Toll signaling pathway. *Drosophila* and human Tolls activate an NF-κB signaling pathway that induces antimicrobial immune response genes. *Drosophila* Toll also activates ventral genes in early embryos. Dorsal and Dif are homologues of NF-κB; Dorsal is critical for inducing ventral genes in fly embryos, while Dif turns on immune response genes in adult flies.